

**SUMMARY OF THE U.S. EPA WORKSHOP  
ON THE RELATIONSHIP BETWEEN  
EXPOSURE DURATION AND TOXICITY**

*Prepared for:*

**U.S. Environmental Protection Agency  
Risk Assessment Forum  
401 M Street SW  
Washington, DC 20460**

**Contract No. 68-D5-0028  
Work Assignment No. 98-10**

*Prepared by:*

**Eastern Research Group  
110 Hartwell Avenue  
Lexington, MA 02421-3136**

**September 30, 1998**

## CONTENTS

<b>SECTION ONE: BACKGROUND . . . . .</b>	<b>1-1</b>
1.1    Background . . . . .	1-1
1.2    The August 1998 Workshop . . . . .	1-1
<b>SECTION TWO: OPENING PLENARY SESSION . . . . .</b>	<b>2-1</b>
2.1    Introductory Presentations . . . . .	2-1
2.2    C × T: Historical Perspectives, Current Issues, and Approaches . . . . .	2-2
2.2.1    The Risk Assessment Context . . . . .	2-2
2.2.2    Haber's Law . . . . .	2-3
2.2.3    Dose Metrics . . . . .	2-7
2.2.4    Historical Perspective on Dose-Response Assessment . . . . .	2-12
2.2.5    Harmonization of "Noncancer" versus "Cancer" Endpoints . . . . .	2-13
2.2.6    Variability and Uncertainty . . . . .	2-17
2.2.7    Discussion Questions . . . . .	2-17
<b>SECTION THREE: PLENARY PRESENTATIONS—ENDPOINTS OF TOXICITY . . . . .</b>	<b>3-1</b>
3.1    Developmental Toxicity: The Effects of Temperature and Exposure on In Vitro Development and Response-Surface Modeling of Their Interaction . . . . .	3-1
3.2    C × T and Dermal Toxicity . . . . .	3-7
3.3    Neurotoxic Effects of Trichloroethylene Inhalation as a Function of Exposure Concentration, Duration, and Target Tissue Dose . . . . .	3-10
3.4    Respiratory Toxicity: Coherent Response Models of Ozone Injury in Humans and Animals .	3-15
3.5    Observer Comments . . . . .	3-26

<b>SECTION FOUR: PLENARY PRESENTATIONS—STATISTICAL APPROACHES</b>	4-1
4.1    What Can Mechanisms Tell Us About Modeling Dose-Time Relationships?	4-1
4.2    C × T Issues Related to National Ambient Air Quality Standards (Eco Effects)	4-6
4.3    Statistical Models for Assessing Dose-Rate Effects	4-9
4.3.1    Background	4-9
4.3.2    Ethylene Oxide Study	4-12
<b>SECTION FIVE: PLENARY PRESENTATIONS—DOSIMETRY AND MECHANISTIC MODELING</b>	5-1
5.1    Dosimetry: Mechanistic Determinants of Exposure-Dose-Response	5-1
5.2    Dosimetry and Mechanistic Modeling	5-11
<b>SECTION SIX: PLENARY PRESENTATIONS: IMPLICATIONS FOR RISK ASSESSMENT</b>	6-1
6.1    Implications for Risk Assessment	6-1
6.2    Integration of Approaches	6-9
<b>SECTION SEVEN: FUTURE DIRECTIONS—WHAT SHOULD BE ACCOMPLISHED IN THE NEXT 5 YEARS?</b>	7-1
<b>SECTION EIGHT: SUMMARIES OF BREAKOUT GROUP DISCUSSIONS</b>	8-1
8.1    Summary of Breakout Group One Discussions	8-1
8.1.1    Relationship Between Concentration and Exposure Duration (C × T) and Toxic Endpoint	8-1
8.1.2    Mechanistic Modeling	8-3
8.1.3    Statistical Modeling	8-5
8.14    Dose Metric	8-5

8.1.5	Risk Assessment . . . . .	8-6
8.2	Summary of Breakout Group Two Discussions . . . . .	8-7
8.2.1	Endpoints of Toxicity . . . . .	8-7
8.2.2	Statistical Approaches . . . . .	8-9
8.2.3	Dosimetry and Mechanistic Modeling . . . . .	8-10
8.2.4	Implications for Risk Assessment . . . . .	8-10
8.3	Summary of Breakout Group Three Discussions . . . . .	8-11
8.3.1	Dosimetry and Mechanistic Modeling . . . . .	8-11
8.3.2	Risk Assessment . . . . .	8-12

**APPENDIX A:**                   **WORKSHOP AGENDA**

**APPENDIX B:**                   **CHARGE TO PARTICIPANTS**

**APPENDIX C:**                   **LIST OF INVITED PARTICIPANTS AND BIOGRAPHIES, LIST OF  
EPA PARTICIPANTS, AND LIST OF OBSERVERS**

**APPENDIX D:**                   **ISSUES PAPER**

